IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : Vanden Heuvel, et al.
SERIAL NO. : 09/555,987
FILED : September 11, 2000
FOR : Methods and Compositions for Treating Diabetes
GROUP ART UNIT : 1617
EXAMINER : Sang Ming Hui

DECLARATION OF DR. JOHN VANDEN HEUVEL

I, John Vanden Heuvel, declare as follows:

1. I am a co-inventor of the subject matter of the above-referenced patent application.

2. I am a citizen of the United States of America.

3. In 1986, I received a B.S. degree in Pharmacology/Toxicology from the University of Wisconsin in Madison, Wisconsin.

4. In 1991, I received a Ph.D. degree in Environmental Toxicology from the University of Wisconsin in Madison, Wisconsin.

4. Since 1987, I have been involved in the investigation and research in molecular toxicology and on the mechanistic basis for adverse effects of exogenous chemicals on biological systems and more recently his research has been focusing on on the peroxisome proliferators – activated receptor (PPAR). In particular, in my research laboratory, I have conducted and supervised research into the mechanism of action of conjugated linoleic acid (CLA), including its activation of PPAR and other biological effects.

5. I am submitting this declaration in support of the patentability of the subject matter of the above-referenced patent application as well as the June 5, 2004 declaration of Dr. Martha Belury.

6. I am presently Associate Professor in the Department of Veterinary Science and Center for Molecular Toxicology, Penn State Univerisity, University Park, Pennsylvania. I have held this position since 2000.

7. Since early in 2004, I have been the Program Coordinator of the Toxicology Undergraduate Program, Penn State University, University Park, Pennsylvania.

8. From 2004 until the present, I have been the Co-Director in the Center for Excellence in Nutrigenomics, Penn State University, University Park, Pennsylvania.

9. From 1997 until 2000, I was an Assistant Professor in the Department of Veterinary Science and Center for Molecular Toxicology, Penn State University, University Park, Pennsylvania.

10. From 1993 until 1996, I was Assistant Professor in the Department of Pharmacology and Toxicology, Purdue University, West Lafayette, Indiana.

11. From 1991 until 1993, I was an Intranural Research Training Award Fellow and Postdoctoral Research Scientist, National Institute of Environmental Health sciences, Laboratory of Biochemical Risk Analysis, Research Triangle Park, North Carolina.

12. From 1987 until 1991, I was a Research Assistant and NIEHS trainee, at the Environmental Toxicology Center, University of Wisconsin-Madison.

63. I have been an invited scientific speaker in numerous scientific meetings or symposia or individually at several universities.

14. I have received more than 20 scientific grants, commissions or contracts

since 1994 for scientific investigations.

75. I am or have been a member or officer of a number of Professional and learned societies including:

The Society of Toxicity
The Molecular Biology Specialty Section, Society of Toxicology
Society of Toxicology Molecular Biology Specialty Section
American Association for the Advancement of Science
American Association of Cancer Research
American Society for Biochemistry and Molecular Biology (ASBMB)

16. I am or have been an ad-hoc reviewer of the following professional journals:

Archives of Biochemistry and Biophysics

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Archives of Biochemistry and Biophysics
Cancer Research
Carcinogenesis
Chemico-Biological Interactions
Fundamental and Applied Toxicology
Toxicology and Applied Pharmacology
Toxicology Letters
Chemical Research in Toxicology
Toxicological Sciences

16. I have also ben an ad-hoc review of grant applications for the Ohio Cancer Research Associates (1994), the World Cancer Research Fund (1999), National Institute of Health (1999 and 2004), the Crohn's and Colitis Foundation of Canada (2000), the United States Department of Agriculture (2000), The Oiled Wildlife Care Network (19976-98), Texas A & M

University (2003), The Eli and Edythe L. Broad Foundation (2003).

17. I have published over 50 scientific papers, 3 books, more than 17 chapters or parts of books on a number of scientific subjects many of which relate to the mechanism of CLA and/or PPAR.

18. I am familiar with and am a co-inventor of the subject matter of United States patent application serial number 09/555,987, which claims are directed to the treatment of type II diabetes mellitus in a diabetic patient comprising administering an effective amount of conjugated linoleic acid to that patient. Thus, the present invention relates to the unexpected finding that the use of conjugated linoleic acid will favorably influence glucose metabolism in diabetic patients and can be used to treat type II diabetes mellitus in a diabetic patient. I understand that the Examiner has rejected the in the patent application as being obvious over a combination of references which the Examiner has interpreted in combination, to teach that conjugated linoleic acid can be used to treat the specific symptoms of type II diabetes mellitus. I am filing my declaration in this application in support of Dr. Martha Belury's June, 2004 declaration and to point out several unsupportable conclusions drawn by Examiner Hui in arguing that the present application is unpatentable.

19. From reading the office action dated September 22, 2004, I understand that the Examiner has essentially made the argument that the claimed invention is unpatentable because it is obvious over the combined teachings of de Boer, et al., U.S. patent number 5,518,751 ("de Boer"), in view of Cook, et al., U.S. patent number 5,554,646 ("Cook") and the article *Diabetes Mellitus* in Pharmacotherapy: A Pathophysiologic Approach, 2nd Ed. 1992, pp. 1121-1127 ("Francisco") render the claimed invention unpatentable as being obvious.

22. I have reviewed the disclosures of de Boer, Cook and Francisco. With respect to De Boer, De Boer is primarily directed to a method for including certain unsaturated

fatty acids into milk products to prevent them from becoming rancid. The major discussion of de Boer is really irrelevant to the presently claimed invention and I believe that the Examiner's interpretation of De Boer is not supported by the facts of which I am aware. The only relevant disclosure in de Boer is that which appears in de Boer in column 1 at lines 35-42. That disclosure is set forth below in italics:

> *An important reason for enriching milk or milk powders with fats containing a high percentage of unsaturated fatty acids or strongly unsaturated fatty acids is to prevent or reduce cardiovascular diseases, atopies, rhumatic disorders or diabetes. In particular, such products contain a high percentage of oleic acid, linoleic acid* ***which may or may not be conjugated****, α-linolenic acid and unsaturated C_{20} and C_{22} fatty acids.* (Emphasis added)

23. The argument that the Examiner makes that de Boer teaches the use of CLA as a treatment for CLA is simply not justified, because to make that argument, one must assume that CLA works to treat diabetes, because the other fatty acids, and in particular, linoleic acid, posited by deBoer to have the same activity as linoleic acid, are also useful. This, however is an unsupportable statement because not all unsaturated fatty acids are effective against diabetes and in particular, linoleic acid is not effective against diabetes mellitus type II and may even be deleterious to that disease state. In my experience, the type of fat in the diet, in particular the saturation and structure of the fatty acid component, dramatically impacts coronary heart disease (CHD) and type 2 diabetes. For example, all three major classes of fatty acids (saturated, monounsaturated, and polyunsaturated) increase high-density lipoprotein (HDL) cholesterol in humans; however, saturated fatty acids increase and polyunsaturated fatty acids (PUFAs) decrease low-density lipoprotein (LDL) cholesterol. The increased ratio of LDL to HDL in the case of saturated fats is associated with increased risk of developing CHD and type 2 diabetes. Saturated fatty acids are generally considered atherogenic and increase thrombosis. Trans fatty acids, found in vegetable shortenings and deep-fried food, raise LDL to HDL ratios to a much greater degree than saturated fats. Two PUFAs that cannot be made in the body (and both of which are essential fatty acids) are linoleic acid (LA, an n-6 fatty acid) and alpha-linolenic acid

(ALA, an n-3 fatty acid).1 Once in the body, LA and ALA may be converted to other PUFAs such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Thus, it is the nature of the structure of the PUFA and whether it is an n-3 PUFA or an n-6 PUFA, which establishes its usefulness for treating CHD and/or type II diabetes.

24. Although many fats have been associated with increasing the risk of CHD (eg, saturated and trans fatty acids), EPA and DHA have been associated with a variety of beneficial health effects. For this reason, diets that are high in ALA, EPA, and DHA (all n-3 PUFAs) have been sought, and these diets include fish oils, flaxseed, mustard seeds, soy beans, walnut oil, and green leafy vegetables. Diets that are high in n-6 PUFAs (linoleic acid and arachidonic acid) are not desirable because these fatty acids are associated with increased LDL levels and they have negligible or deleterious influence on type II diabetes. Dr. Martha Belury, the coinventor of the subject matter of the present application has previously submitted her declaration which shows that linoleic acid (an n-6 PUFA) does not produce any significant impact on type II diabetes. Based upon Dr. Belury's experimental results, n-6 PUFAs have little impact on type II diabetes and may be deleterious. For that reason, n-6 PUFAs, such as linoleic acid and arachidonic acid, which are disclosed by De Boer as having significant activity against diabetes (arachidonic acid is an n-6, C_{20} PUFA), in reality do not. Moreover, as will be explained below, it was known at the time of deBoer and the present invention, that linoleic acid did not have favorable activity in treating glucose intolerance and insulin symptoms of diabetes type II. In addition, monosaturated fatty acids such as oleic acid (disclosed by deBoer) also do not have activity against diabetes. Yet, the Examiner has interpreted de Boer disclosure for teaching that all of the fatty acids disclosed therein, including the cited n-6 PUFAs (linoleic and arachidonic acid), which are known to have no effect or deleterious effects, have beneficial effects against type II diabetes. This is simply not accurate.

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1 N-3 PUFAS have multiple double bonds the first of which is found at carbon position 3-4 measured from the ω end (non-carboxylic end) of the fatty acid. N-6 PUFAs have multiple double bonds the first of which is found at

25. Conjugated linoleic acid (CLA) collectively refers to a group of LA derivatives with several positional (double bonds in carbon 9 and 11 or 10 and 12) and geometric (cis, Z and trans, E) isomers. CLAs fall within the same family of PUFAs as linoleic and arachidonic acid and all are characterized as being n-6 PUFAs. CLAs are relatively abundant in ruminant meat and heat-processed dairy products. Although CLA is an n-6 polyunsatured fatty acid, and would be expected to either not be useful or to be deleterious for treating diabetes type II based upon the fact that other n-6 PUFAs, especially the closely related linoleic acid, exhibit no activity or deleterious consequences for treating diabetes type II, it is evident from animal studies that we and others have performed recently, that CLA has effects on CHD and diabetes that resemble or are superior to those of n-3 PUFAs. This is a completely unexpected finding.

26. The question that remains is why some PUFAs, in particular n-3 PUFAs (ALA, EPA, and DHA) and CLAs, are associated with reduced risk of CHD whereas closely related n-6 PUFAs (LA and AA), and monosaturated (oleic acid) and saturated (palmitic acid) fatty acids are either not as effective as are the n-3 PUFAs or are detrimental to heart health and diabetes. One explanation is that cognate receptors exist that preferentially respond to a particular structure of fatty acid. Over the past eight years, we have generated considerable data showing that CLA may exert its beneficial effects via the nuclear receptor PPARγ. This receptor is activated by the "good" fatty acids (n-3 PUFAs, CLA) to a much greater extent than by the "bad" fatty acids (n-6 PUFAs, unsaturated, monounsaturated). Attached hereto is a reprint of a review article that we have published recently that has a full list of citations to back up our contention. See, Vanden Heuvel, J.P. (2004) Diet, fatty acids and genes important for heart disease. Curr Atheroscler Rep 6, 432-40, enclosed.

27. The Examiner interprets DeBoer as supporting the contention that unsaturated fatty acids in general, including oleic, linoleic, CLA and arachidonic acid fatty acids are all useful for treating diabetes. A review of epidemiological data shows that monounsaturated fatty acids

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carbon position 6-7.from the ω end

such as oleic acid and n-6 PUFAs (linoleic and by extension, arachidonic acid, also an n-6 PUFA) are not effective. See, Renaud S and Lanzmann-Petithory D: Coronary heart disease: dietary links and pathogenesis. *Pub Health Nutr* 2001, 4:459–474; and Hu and Willett: Optimal diets for prevention of coronary heart disease. *JAMA* 2002, 288:2569–2578, both of which are enclosed. Also enclosed are three prior art references (the first reference is prior art even as to de Boer) which clearly show that linoleic acid, an n-6 PUFA, and monounsaturated fatty acids, such as oleic acid, are either inactive or actually deleterious in the treatment of symptoms of type II diabetes mellitus. See, Ikemoto, et al., *Metabolism.* 1996 Dec;45(12):1539-46; Heine, et al., *Am J Clin Nutr.* 1989 Mar;49(3):448-56; and Simopoulos, *Free Radic Biol Med.* 1994 Oct;17(4):367-72, enclosed. See also, Blankenshorn, et al., *JAMA*, 263, pp. 1846-1852, 1990; and Hodgson, et al., *Am. J. Clin. Nutr. 58, 228-234, 1993* and related letters to the editor, which evidence that linoleic acid contributes to coronary heart disease. Thus, deBoer, read in light of contemporaneous scientific studies, cannot be reasonably interpreted to support the view that all disclosed fatty acids can be used to treat diabetes. In fact, of the fatty acids disclosed, the fatty acid closest in structure to CLA is linoleic acid, which was shown in the prior art to be inactive. Thus, based upon the fact that it was known in the art that linoleic acid was not effective to treat diabetes, the most reasonable interpretation is that CLA, an n-6 PUFA closely related in structure to linoleic acid, would likely be inactive as well. In fact, if one would have predicted the effects of CLA on diabetes based on that prior art, the obvious conclusion to be drawn is that CLA would not have a beneficial effect on diabetes. Given this prior art teaching, the only reasonable interpretation of the de Boer teachings is that CLA may be useful for treating the same disease states as linoleic acid, but ***not*** diabetes, because linoleic acid is inactive or deleterious against diabetes.

28. It is clearly non-obvious from De Boer, when read in light of the contemporaneous prior art, to use CLA to treat type II diabetes mellitus because the structural family of fatty acids (n-6 PUFAs) to which CLA belongs, and a closely related fatty acid, linoleic

acid, was known at the time of the present invention to be inactive for treating diabetes, but not for the other disease states cited in de Boer.

29. The Examiner has also cited the teachings of Cook against the present invention. I do not believe that Cook adds anything to the teachings of De Boer. Cook's teachings are directed to the use of CLA to decrease body fat and increase the protein content primarily of meat animals to be slaughtered for food. There is absolutely no teaching in Cook that CLA may be used to treat diabetes *of any kind*, especially type II diabetes mellitus. In addition, there is absolutely no disclosure in Cook as to how CLA may be reducing body fat and increasing the body protein content. The use of CLA to decrease body fat and increase body protein in animals as taught by Cook is readily distinguishable from the use of CLA to treat type II diabetes mellitus. Many individuals who have low body fat content have high plasma triglyceride and free fatty acid levels, and many individuals with high body fat have normal triglyceride and free fatty acid levels. There is no causal connection between these conditions. The mere fact that Cook teaches a reduction in body fat and increase in body protein in normal animals does not suggest in any way the administration of CLA in a type II diabetes mellitus patient to lower elevated plasma triglyceride and/or free fatty acid levels. Nor do the teachings of Cook have any connection to any of the other symptoms of type II diabetes mellitus which are treated by the present invention. Consequently, I believe that it is not obvious to use CLA to treat type II diabetes mellitus from the combined teachings of de Boer, in view of Cook.

29. I understand that the Examiner also has rejected the previously filed claims 1-22 based upon his view that the claimed subject matter is obvious over the further teachings of Francisco, when combined with the teachings of de Boer and Cook. From Francisco, there is absolutely no suggestion of the use of CLA to treat type II diabetes mellitus. Francisco does suggest that diet may play a role in both type I and type II diabetes mellitus and does generally disclose certain symptoms of diabetes. However, the only relevant section of Francisco with respect to the type of fatty acid to be used is found on page 1125 in the second column where

Francisco indicates that the amount and type of fatty acids may influence diabetes. However, Francisco indicates that no more than about 30% of the caloric intake in a diet of a diabetic patient should be derived from fat (p. 1125 second column, lines 3-5) and that 1/3 of that caloric content should be from saturated fat (10%), polyunsaturated fat (10%) and the rest from monosaturated fat. This passage in Francisco neither points to the use of CLA for the treatment of diabetes nor does it suggest the type of fatty acid which is to be used, which, as discussed above, is critical to the treatment of diabetes. Indeed, as explained above, if a diabetic person followed the teachings of de Boer and Francisco and chose a combination of saturated fats, monounsaturated fats (oleic acid) and n-6 polyunsaturated fats (linoleic acid or arachidonic acid) as disclosed by de Boer, this would have no effect or actually *prove deleterious* to the treatment of diabetes in the individual being put on that diet. Thus, Francisco does not provide any relevant teaching which points to the use of CLA for treating type II diabetes mellitus and its general teachings represents a perspective which is clearly deficient and not even accurate. Because Francisco is silent as to the type of fatty acid to be used, it is completely deficient in suggesting that somehow CLA is particularly effective when used to treat type II diabetes mellitus.

30. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: January 19, 2005

John Vanden Heuvel, Ph.D.